UT Southwestern
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Cognitive Dysfunction and MDD

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Overview

- Assessing cognitive function in MDD
- Prevalence and characteristics of cognitive symptoms in MDD
- Treatment considerations
- What are the functional consequences of cognitive deficits in MDD?
- Is there a mismatch between changes in symptoms and cognition?
- Next steps in the field

Prevalence of Major Depressive Disorder (MDD)

- MDD affects 5-7% of adults every year
- During their lifetime, 13-16% of adults will have one or more major depressive episodes
- Over one-quarter of MDD patients report not having even a single asymptomatic week during follow-up lasting up to 12 years
- For most patients, MDD is chronic and/or recurrent
- For most MDD patients, depression starts in second or third decade of life and impairs work productivity

Burden of MDD

- One of the leading causes of disability worldwide
- Globally, MDD accounts for one-tenth of all-years-lived-with disability YLD)
- By 2020, MDD is projected to be the second leading cause of disability
- In the United States, disability associated with MDD has increased 40% over the last two decades

Major Depressive Episode: DSM-5 Diagnostic Criteria

- Depressed mood (core symptom; in children and adolescents, can be irritable mood)
- Diminished interest/pleasure in activities (core symptom)
- Major change in appetite or weight
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness/excessive guilt
- **Diminished ability to concentrate or indecisiveness**
- Recurrent thoughts of death, dying, or suicide

APA *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. 2013.

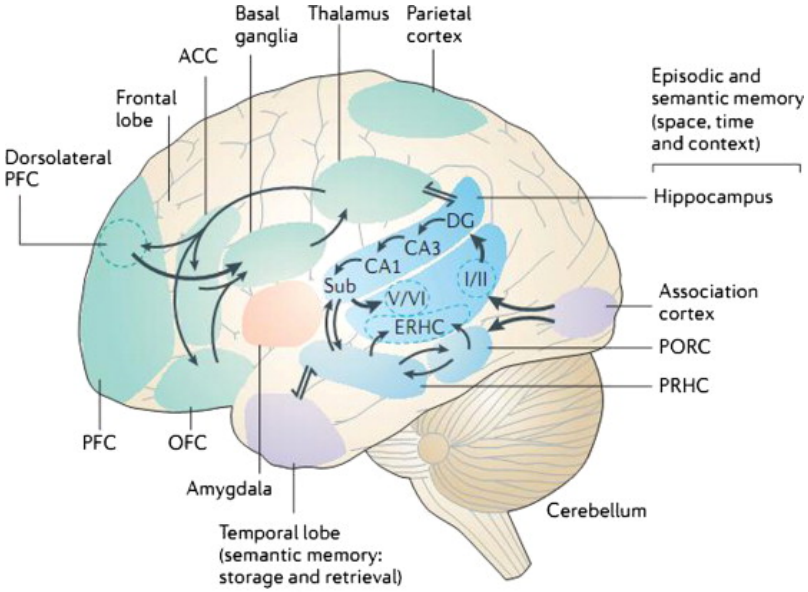
Prevalence and Characteristics of Cognitive Deficits in MDD

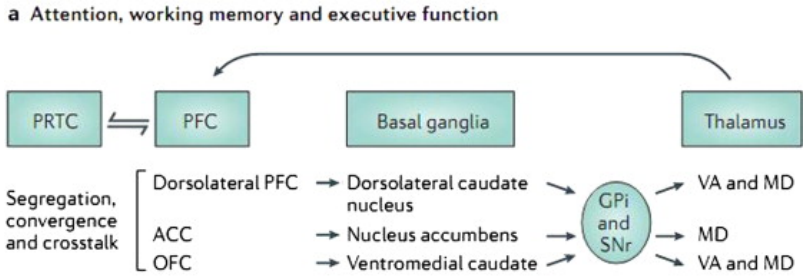
Cognitive function and MDD

Frequently observed with MDD in following domains:

- Attention
- Verbal learning
- Non verbal learning
- Memory
- Executive functioning

Neural Circuits Involved in Cognition





Millan, et al., *2012.Nat Rev Drug Discov.* Feb 1;11(2):141-68. doi: 10.1038/nrd3628

Objective Measures of Impaired Cognition in Depression

	Endogenous (20)	Neurotic (20)	Control (20)	*P* value for F test	Scheffe ($P < 0.05$)
Sum 5 AVLT Trials	40.5 (12.0)	44.0 (8.2)	55.8 (11.2)	0.0001	C > N, E
Delayed Recall	8.0 (3.5)	9.2 (4.0)	12.2 (2.9)	0.002	C > N, E
Recognition	9.2 (3.6)	9.4 (6.3)	13.4 (1.9)	0.004	C > N, E
'Forgetting'	2.3 (1.7)	2.4 (2.3)	1.5 (1.5)	0.21	
Digitspan (forward)	9.3 (2.0)	8.8 (1.7)	9.2 (1.9)	0.66	
Digitspan (back)	7.0 (2.2)	6.4 (2.1)	7.8 (2.2)	0.19	
Block design	23.9 (12.8)	29.8 (10.2)	32.1 (11.1)	0.12	
DSST	37.9 (15.0)	45.9 (12.8)	53.7 (10.6)	0.001	C > E
Trails A (secs)	50.7 (24.5)	40.9 (10.1)	35.8 (11.9)	0.02	C < E
Trails B (secs)	144 (85.1)	100.3 (70.3)	68.9 (22.5)	0.002	C < E
Verbal fluency (Words/min.)	12.8 (5.8)	13.2 (6.3)	15.8 (4.8)	0.23	

Scores for the three groups were compared by one way ANOVA. Differences between groups were located post hoc with the Scheffe test; abbreviations are, C = Control group, N = Neurotic group, E = Endogenous group.

Austin et al, *Journal of Affective Disorders*, 1992; 25, 21–29

Neurocognitive Profiles of Depressed Patients with Major Depressive Disorder and Bipolar Disorder

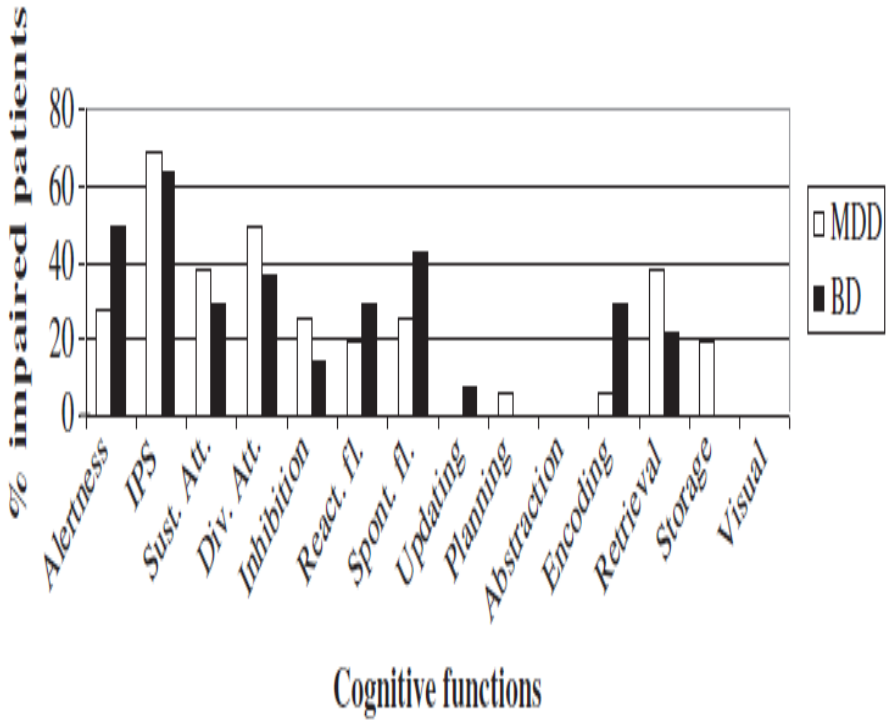
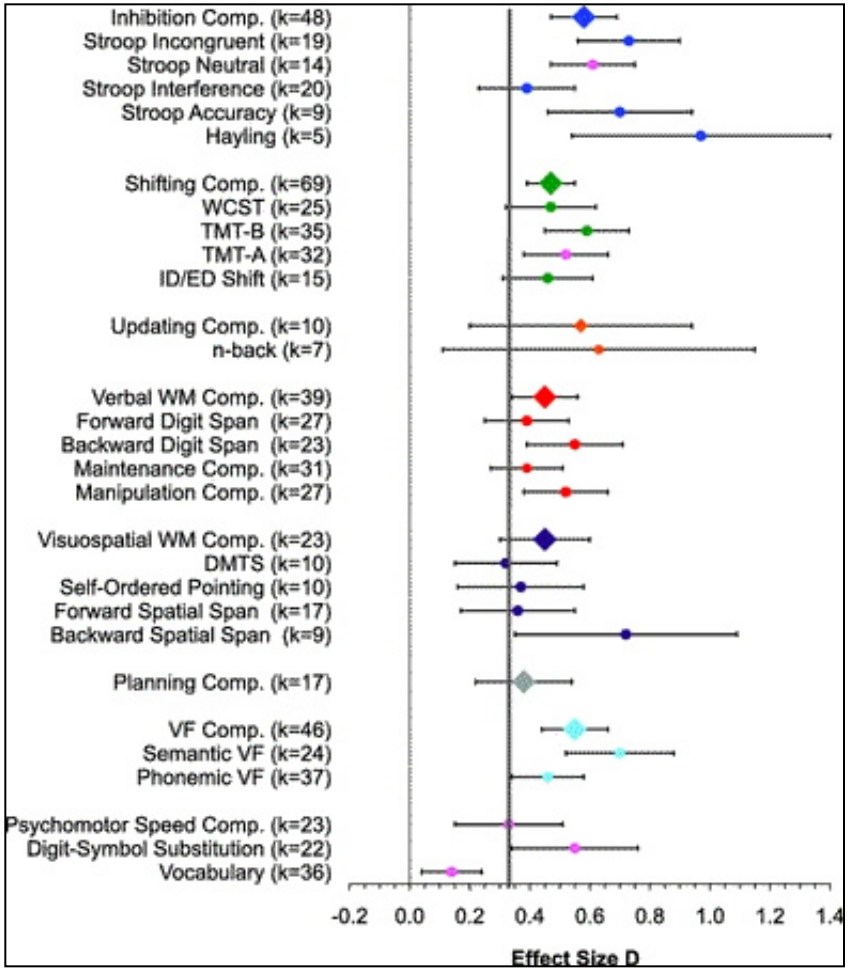


Fig. 1. Percentage of impaired patients in each cognitive function. Information processing speed (IPS), Sustained attention (sust. att.), Divided attention (div. att.), Reactive flexibility (react. fl.), Spontaneous flexibility (spont. fl.), Major depressive disorder (MDD), Bipolar disorder (BD).

J. Godard et al., *Psychiatry Research 190* (2011) 244–252

Meta-Analysis of Studies Using Objective Measures of Executive Function in Depression



Major Depressive Disorder Is Associated With Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review.
Snyder, Hannah

Psychological Bulletin. 139(1):81-132, January 2013.
DOI: 10.1037/a0028727

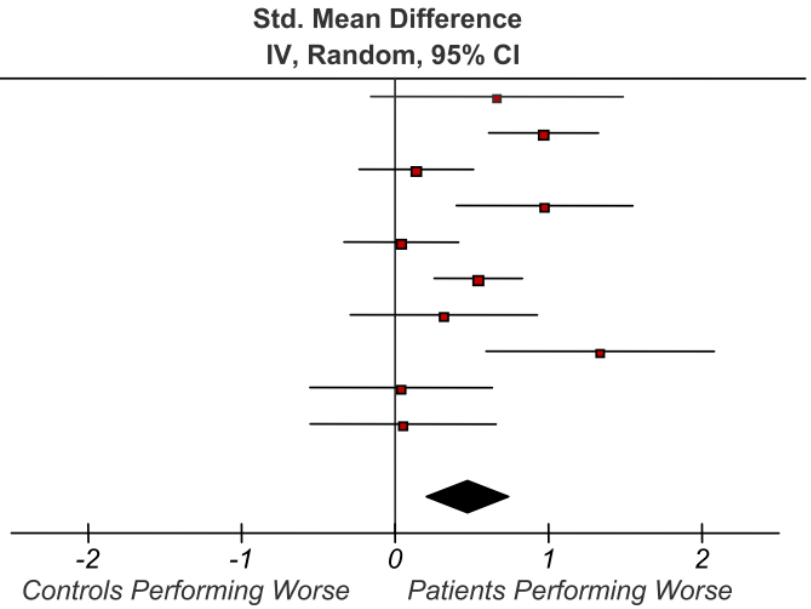
Figure 1 Weighted mean effect sizes for all analyses. Error bars are 95% confidence intervals. Compared to healthy control participants, patients with major depressive disorder are significantly impaired on all tasks. Executive function (EF) composite measures are indicated with diamond symbols, and individual measures within each EF component by circle symbols in the same color. Pink circles indicate non-EF comparison measures. The solid gray vertical line indicates the psychomotor speed composite score effect size: Measures for which the lower error bar (95% confidence interval) does not pass the dashed line are significantly greater than 0, and those that do not pass the solid gray line have significantly larger effect sizes than the psychomotor speed effect size. Comp. = composite score; WCST = Wisconsin Card Sorting Test; TMT-B = Trail Making Test Part B; TMT-A = Trail Making Test Part A; ID/ED = Intradimensional/Extradimensional; WM = working memory; DMTS = delayed-match-to-sample; VF = verbal fluency.

Forest Plot of individual and pooled effect sizes for psychomotor speed

Study (Test)	Weight	Std. Mean Difference IV, Random, 95% CI
Ilonen 2000 (2)	*6.4%*	*0.66 [-0.16, 1.49]*
Reischies 2000 (1)	*12.4%*	*0.97 [0.61, 1.32]*
Grant 2001 (1, 2)	*12.2%*	*0.14 [-0.23, 0.51]*
Neu 2005 (1)	*9.3%*	*0.97 [0.40, 1.55]*
Castaneda 2008a (1, 2)	*12.2%*	*0.04 [-0.33, 0.41]*
Preiss 2009 (1)	*13.5%*	*0.54 [0.26, 0.83]*
Reppermund 2009 (1)	*8.8%*	*0.32 [-0.29, 0.93]*
Kaymak 2010 (1)	*7.2%*	*1.34 [0.59, 2.08]*
van Wingen 2010 (curr) (1, 3)	*9.0%*	*0.04 [-0.55, 0.63]*
van Wingen 2010 (prev) (1, 3)	*8.9%*	*0.05 [-0.55, 0.66]*
Total (95% CI)	**100.0%**	**0.48 [0.21, 0.75]**

Heterogeneity: Chi² = 28.37, df = 9 (P = 0.0008); I² = 68%
Test for overall effect: Z = 3.49 (P = 0.0005)

(1)Trail Making Test A; (2)Digit Symbol-Coding; (3)Symbol Digit Modalities Test

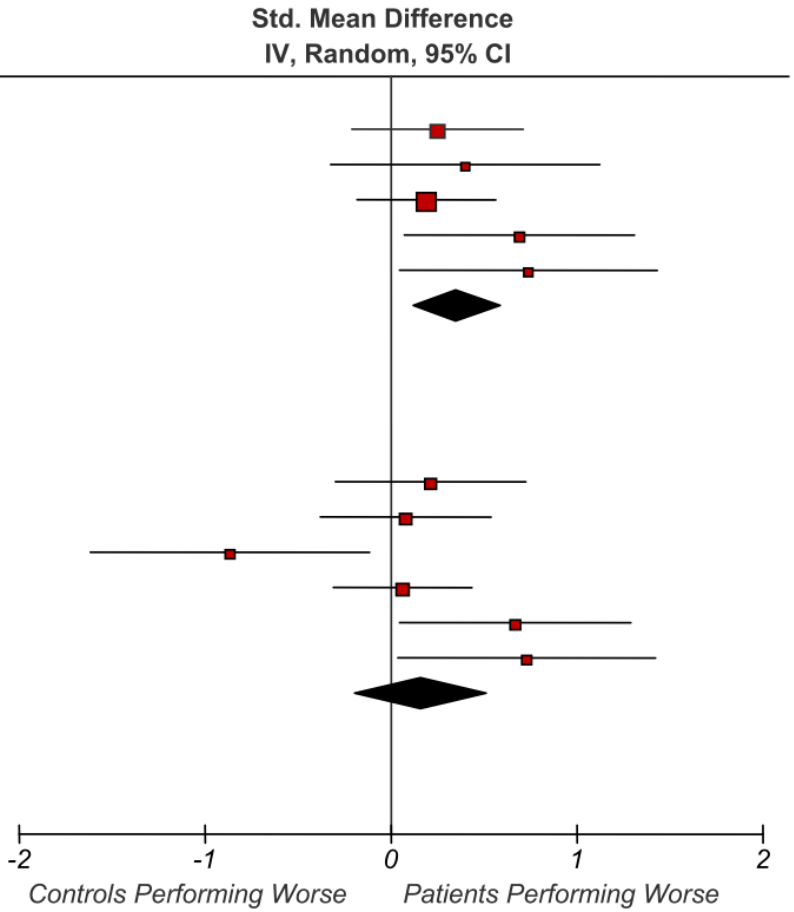


Lee,R.S.C., et al., A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of Affective Disorders*, Volume 140, Issue 2, 2012, 113–124. http://dx.doi.org/10.1016/j.jad.2011.10.023

Forest Plot for individual and pooled effect sizes for attention and working memory

Study (Test)	Weight	Std. Mean Difference IV, Random, 95% CI
Attention		
Fossati 2004 (1)	*25.5%*	*0.25 [-0.21, 0.71]*
Westheide 2007 (1)	*10.3%*	*0.40 [-0.32, 1.12]*
Castaneda 2008a (1, 2)	*38.8%*	*0.19 [-0.18, 0.56]*
Reppermund 2009 (1, 2)	*14.1%*	*0.69 [0.07, 1.31]*
Kaymak 2010 (1)	*11.3%*	*0.74 [0.05, 1.43]*
Subtotal (95% CI)	**100.0%**	**0.36 [0.13, 0.59]**
Heterogeneity: Chi² = 3.28, df = 4 (P = 0.51); I² = 0%		
Test for overall effect: Z = 3.03 (P = 0.002)		
Working Memory		
Ilonen 2000 (3)	*17.8%*	*0.21 [-0.30, 0.72]*
Fossati 2004 (3)	*19.2%*	*0.08 [-0.38, 0.54]*
Westheide 2007 (3)	*12.5%*	*-0.87 [-1.62, -0.12]*
Castaneda 2008a (3, 4)	*21.6%*	*0.06 [-0.31, 0.43]*
Reppermund 2009 (3, 4)	*15.2%*	*0.67 [0.05, 1.29]*
Kaymak 2010 (3)	*13.6%*	*0.73 [0.04, 1.42]*
Subtotal (95% CI)	**100.0%**	**0.16 [-0.20, 0.51]**
Heterogeneity: Chi² = 12.77, df = 5 (P = 0.03); I² = 61%		
Test for overall effect: Z = 0.88 (P = 0.38)		

(1)Digit Span Forwards; (2)Spatial Span Forwards; (3)Digit Span Backwards; (4)Spatial Span Backwards

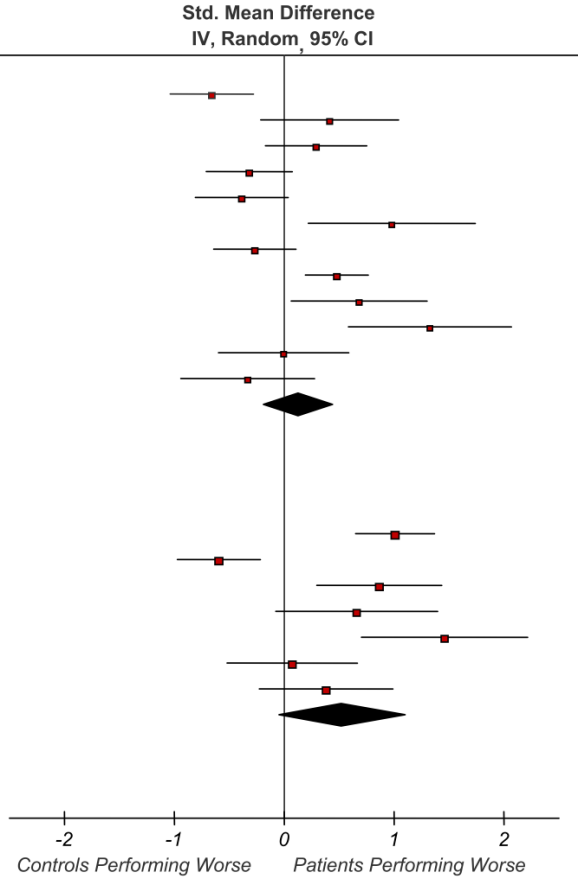


Lee,R.S.C., et al., A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of Affective Disorders*, Volume 140, Issue 2, 2012, 113–124. http://dx.doi.org/10.1016/j.jad.2011.10.023

Forest Plot for individual and pooled effect sizes for verbal, visual learning and memory

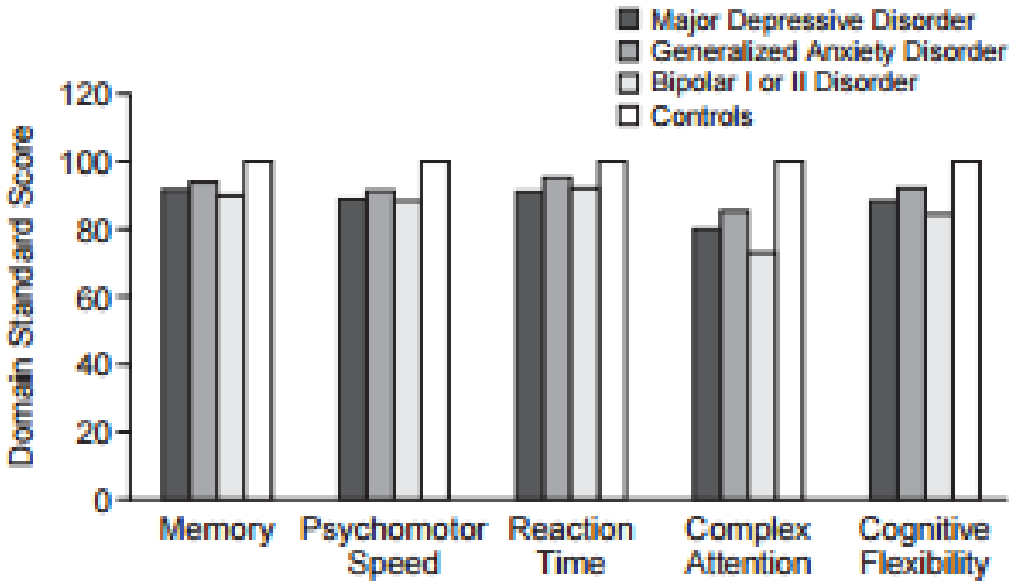
Study (Test)	Weight	Std. Mean Difference IV, Random, 95% CI
Verbal		
Grant 2001 (8, 9)	*9.4%*	*-0.66 [-1.04, -0.28]*
MacQueen 2003 (5)	*7.6%*	*0.41 [-0.21, 1.04]*
Fossati 2004 (10)	*8.8%*	*0.29 [-0.17, 0.75]*
Wang 2006 (curr) (5, 6, 7)	*9.3%*	*-0.32 [-0.71, 0.07]*
Wang 2006 (prev) (5, 6, 7)	*9.1%*	*-0.39 [-0.81, 0.04]*
Westheide 2007 (3, 4)	*6.6%*	*0.98 [0.22, 1.74]*
Castaneda 2008a (5)	*9.4%*	*-0.27 [-0.64, 0.11]*
Preiss 2009 (3, 4)	*9.9%*	*0.48 [0.19, 0.77]*
Reppermund 2009 (1, 2)	*7.6%*	*0.68 [0.06, 1.30]*
Kaymak 2010 (1, 2)	*6.8%*	*1.33 [0.59, 2.07]*
van Wingen 2010 (curr) (3, 4)	*7.8%*	*-0.00 [-0.60, 0.59]*
van Wingen 2010 (prev) (3, 4)	*7.7%*	*-0.33 [-0.94, 0.28]*
Subtotal (95% CI)	**100.0%**	**0.13 [-0.18, 0.45]**
Heterogeneity: Chi² = 57.37, df = 11 (P < 0.00001); I² = 81%		
Test for overall effect: Z = 0.84 (P = 0.40)		
Visual		
Reischies 2000 (14)	*15.7%*	*1.01 [0.65, 1.37]*
Grant 2001 (11, 12)	*15.6%*	*-0.59 [-0.97, -0.22]*
Neu 2005 (14)	*14.4%*	*0.87 [0.30, 1.43]*
Westheide 2007 (11, 12, 14)	*13.1%*	*0.66 [-0.08, 1.40]*
Kaymak 2010 (11, 12)	*13.0%*	*1.46 [0.70, 2.22]*
van Wingen 2010 (curr) (13)	*14.2%*	*0.07 [-0.52, 0.67]*
van Wingen 2010 (prev) (13)	*14.1%*	*0.38 [-0.23, 0.99]*
Subtotal (95% CI)	**100.0%**	**0.53 [-0.05, 1.11]**
Heterogeneity: Chi² = 49.47, df = 6 (P < 0.00001); I² = 88%		
Test for overall effect: Z = 1.80 (P = 0.07)		

(1)Logical Memory 1; (2)Logical Memory 2; (3)RAVLT Total; (4)RAVLT Delayed Recall; (5)CVLT-II Total; (6)CVLT-II Short Delayed Free Recall; (7)CVLT-II Long Delayed Free Recall; (8)HVLT Total; (9)HVLT Delayed Recall; (10)SRT Total; (11)Visual Reproduction 1; (12)Visual Reproduction 2; (13)RCFT Delayed Recall; (14)WMS Visual Memory Index



Lee,R.S.C., et al., A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of Affective Disorders*, Volume 140, Issue 2, 2012, 113–124. http://dx.doi.org/10.1016/j.jad.2011.10.023

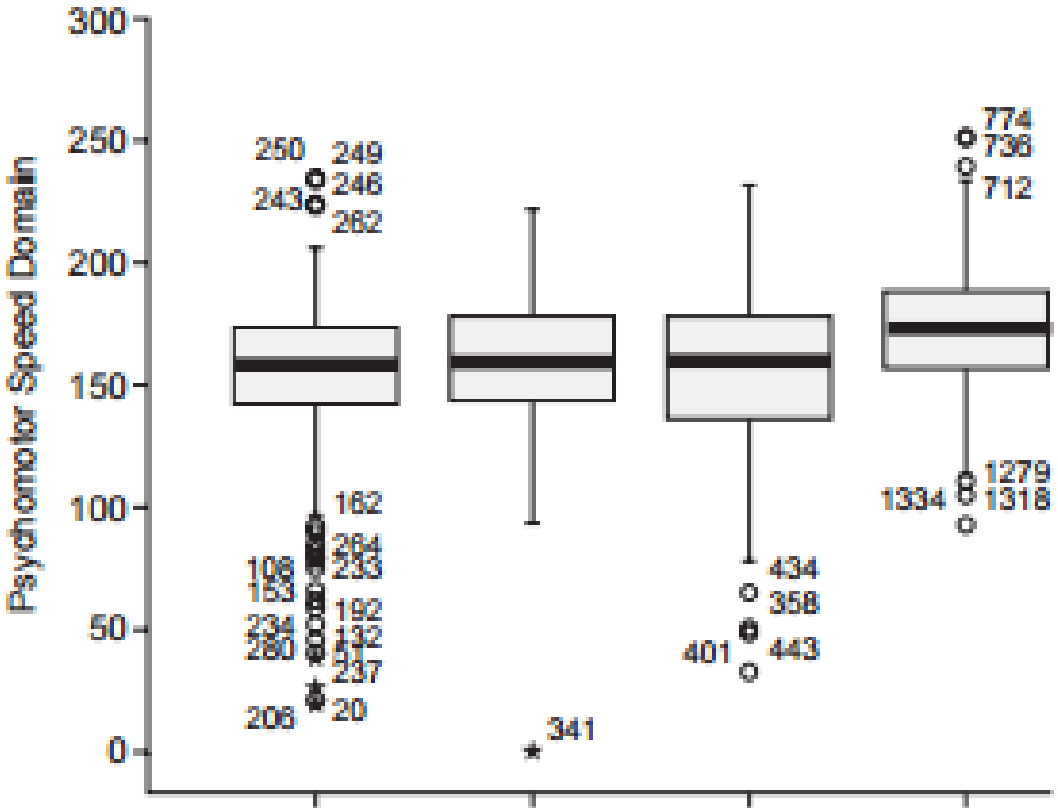
Mean Differences in Cognitive Function between Patient Groups and Controls



The scores for each cognitive domain are standardized, with a mean of 100 and a standard deviation of 15. On this metric, the mean scores of controls are 100.

Modified from Gualtieri CT, Morgan DW. The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *J Clin Psychiatry*. 2008 Jul;69(7):1122-30.

Boxplot Data

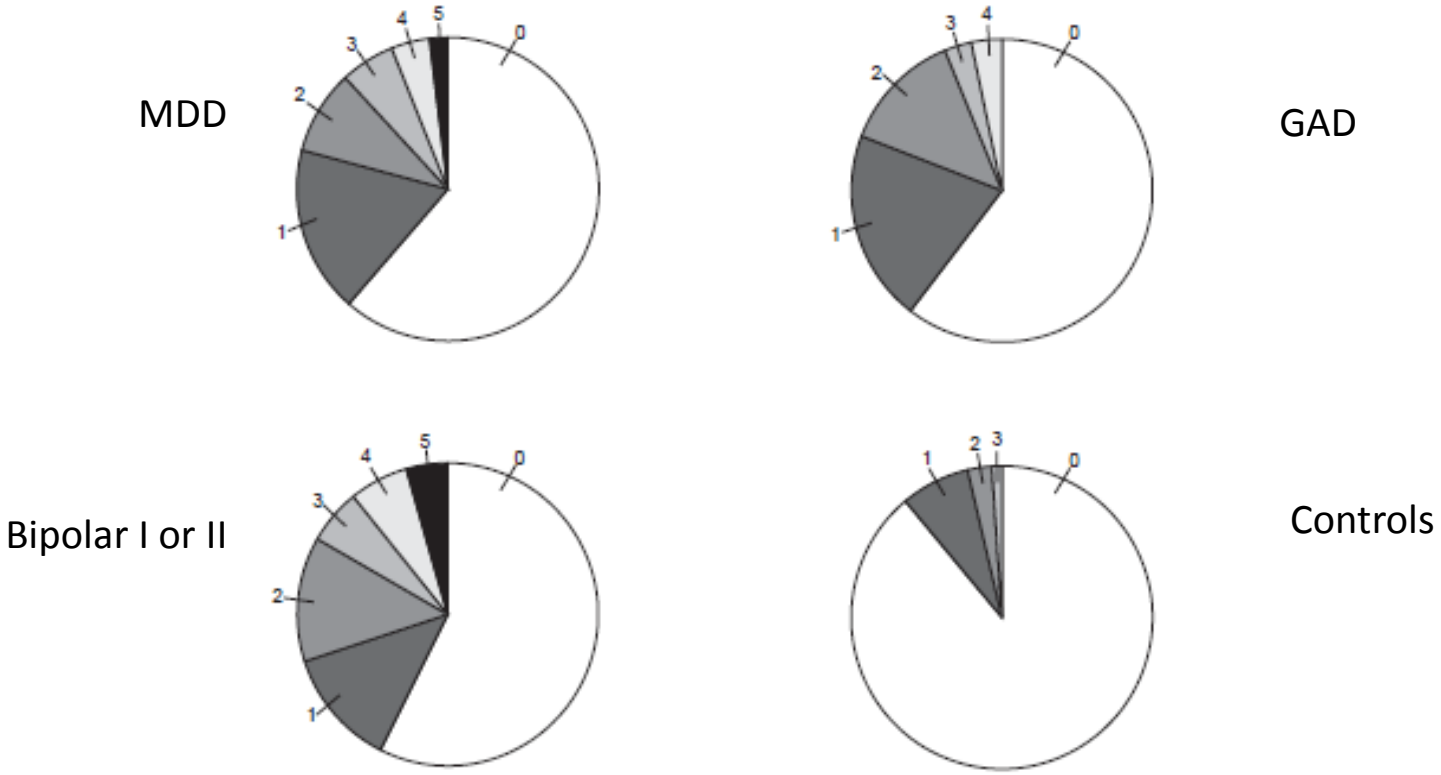


Also show significant overlap in performance between patients and controls, but highlights the increased number of patients with impaired cognition (particularly in MDD)

Stars are outliers more than 2 SDs from the mean; circles are outliers between 1 and 2 SDs from the mean

Modified from Gualtieri CT, Morgan DW. The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *J Clin Psychiatry*. 2008 Jul;69(7):1122-30.

Number of Patients and Controls Scoring 2 SDs or More Below the Mean in the 5 Domains



Frequency of domain scores < 70 among three patient groups and controls

Modified from Gualtieri CT, Morgan DW. The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *J Clin Psychiatry*. 2008 Jul;69(7):1122-30.

Determinants of cognitive deficits in MDD

Determinant
Age
Age at onset
Educational attainment
Baseline depression severity
MDD subtype
Symptomatic status (i.e remission vs non remission)
Psychiatric comorbidity
Medical comorbidity
Illness duration
Episode frequency
Treatment
Childhood Adversity

McIntyre, R.S., et al., *Depress Anxiety*. 2013 Jun;30(6):515-27. doi: 10.1002/da.22063. Epub 2013 Mar 6.

Cognitive Function Changes with Treatment But Residual Symptoms Persist

Cognitive function improves with treatment

- Several treatments have been associated with improved cognition in MDD:
  - Antidepressants (SSRI, SSRE, SNRI, multimodal)
  - Cognitive remediation
  - Exercise
- Few studies have cognition as primary outcomes
- Many studies are preliminary; more studies are needed

Baune BT, Renger L. Pharmacological and non-pharmacological interventions to improve cognitive dysfunction and functional ability in clinical depression--a systematic review. *Psychiatry Res*. 2014 Sep 30;219(1):25-50. doi:10.1016/j.psychres.2014.05.013. Epub 2014 May 14.

Pre-post Cognitive Changes in Several Domains

Table 2

Performance of the MDD patients in the neuropsychological functional tests before and after antidepressant treatment.

	Before treatment	After treatment	*p* values	RCI corrected for practice effects
CPT				
Non-masked	3.7 ± 1.1	4.2 ± 0.9	0.052	–
Masked	2.9 ± 1.2	3.7 ± 0.8	<0.001*	0.4 ± 0.7[a]
FTT				
Dominant finger	37.5 ± 10.8	41.1 ± 12.2	0.111	–
Non-dominant finger	35.8 ± 8.5	39.9 ± 8.4	0.020*	4.2 ± 4.6
WCST				
Completed categories	1.7 ± 1.4	2.2 ± 1.8	0.027*	0.4 ± 0.5[a]
Preservative errors	15.7 ± 13.1	14.2 ± 11.9	0.981	–

MDD: major depression disorder, RCI: reliable change indices, CPT: continuous performance test, FTT: Finger-Tapping Test, WCST: Wisconsin card-sorting test.

* $p < 0.05$.

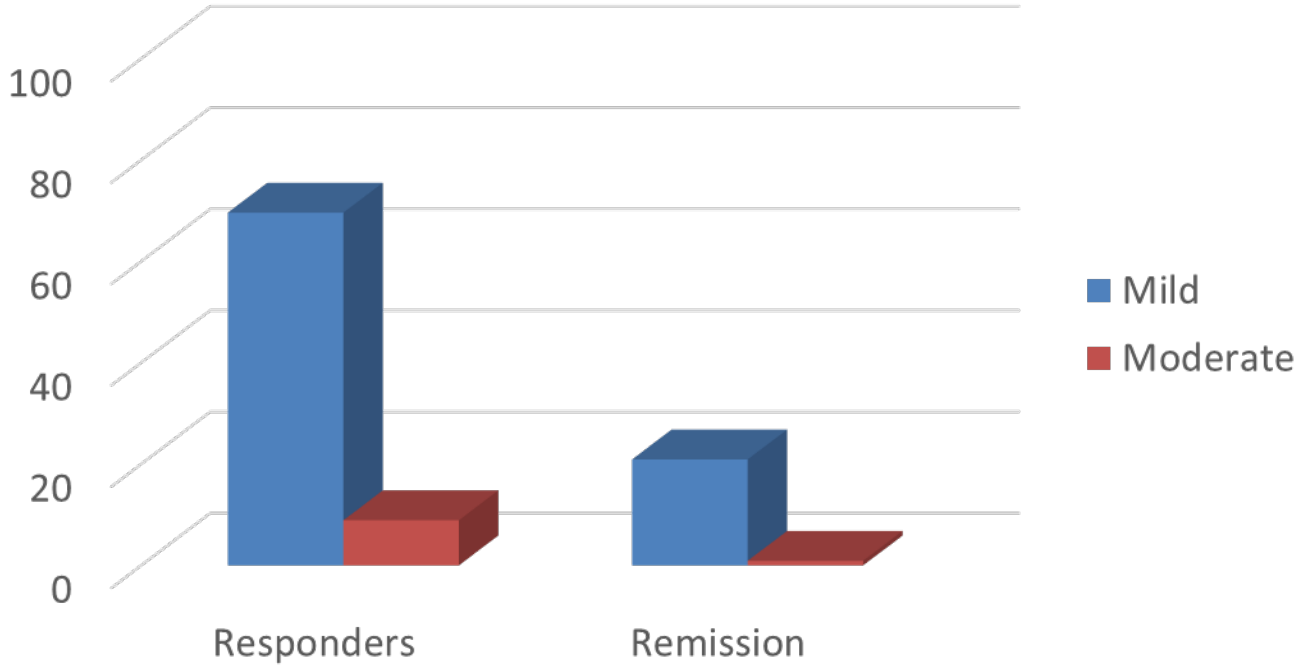
[a] Clinically significant changes.

Chang et al, *Brain, Behavior, and Immunity* 26 (2012) 90–95

Cognitive function is a common residual symptom

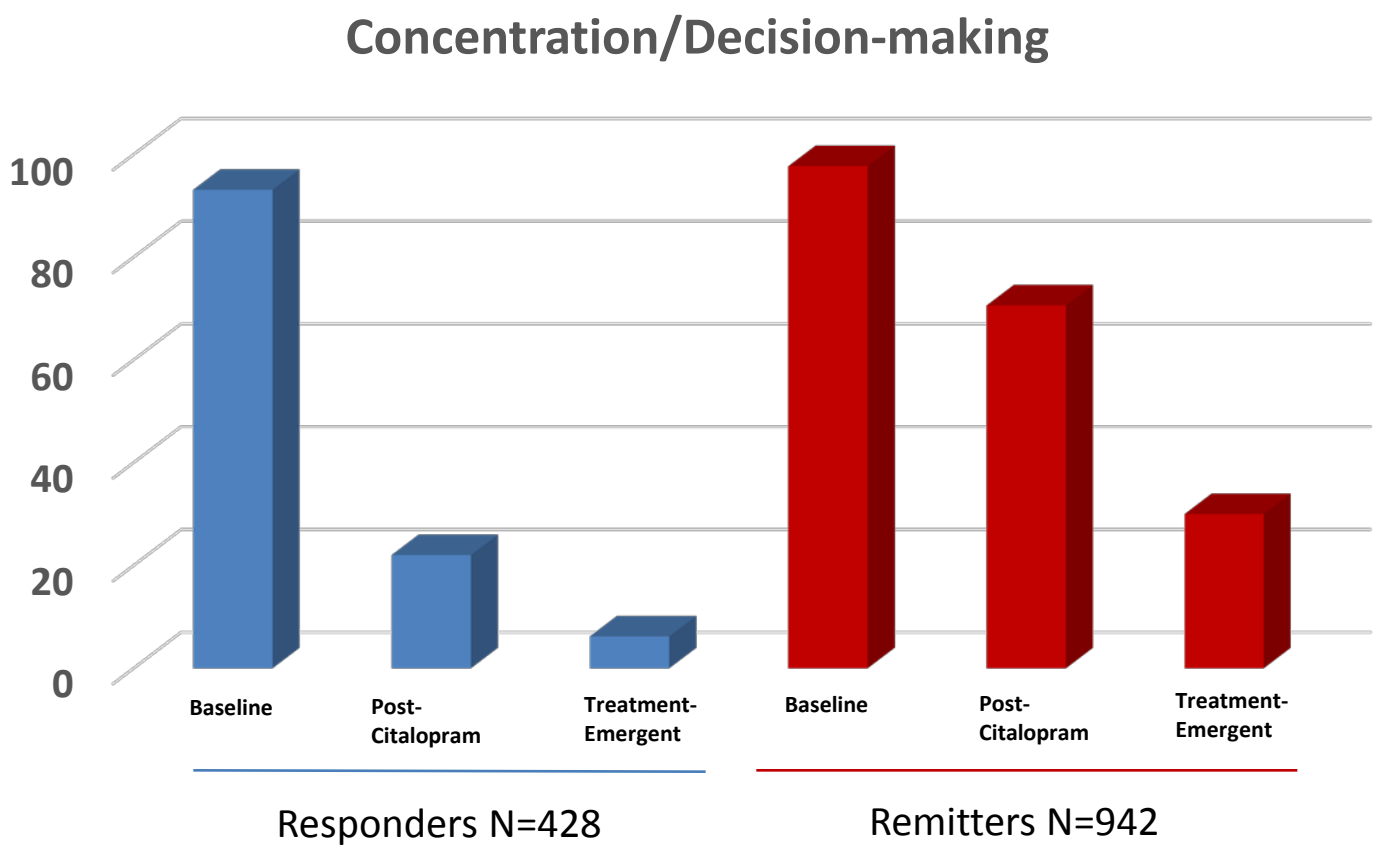
- Several studies indicate residual cognitive function in several domains
- Occurs even in the presence of symptomatic remission

Percent of Citalopram-Treated Individuals with Mild or Moderate Residual Concentration/Decision-Making Difficulty



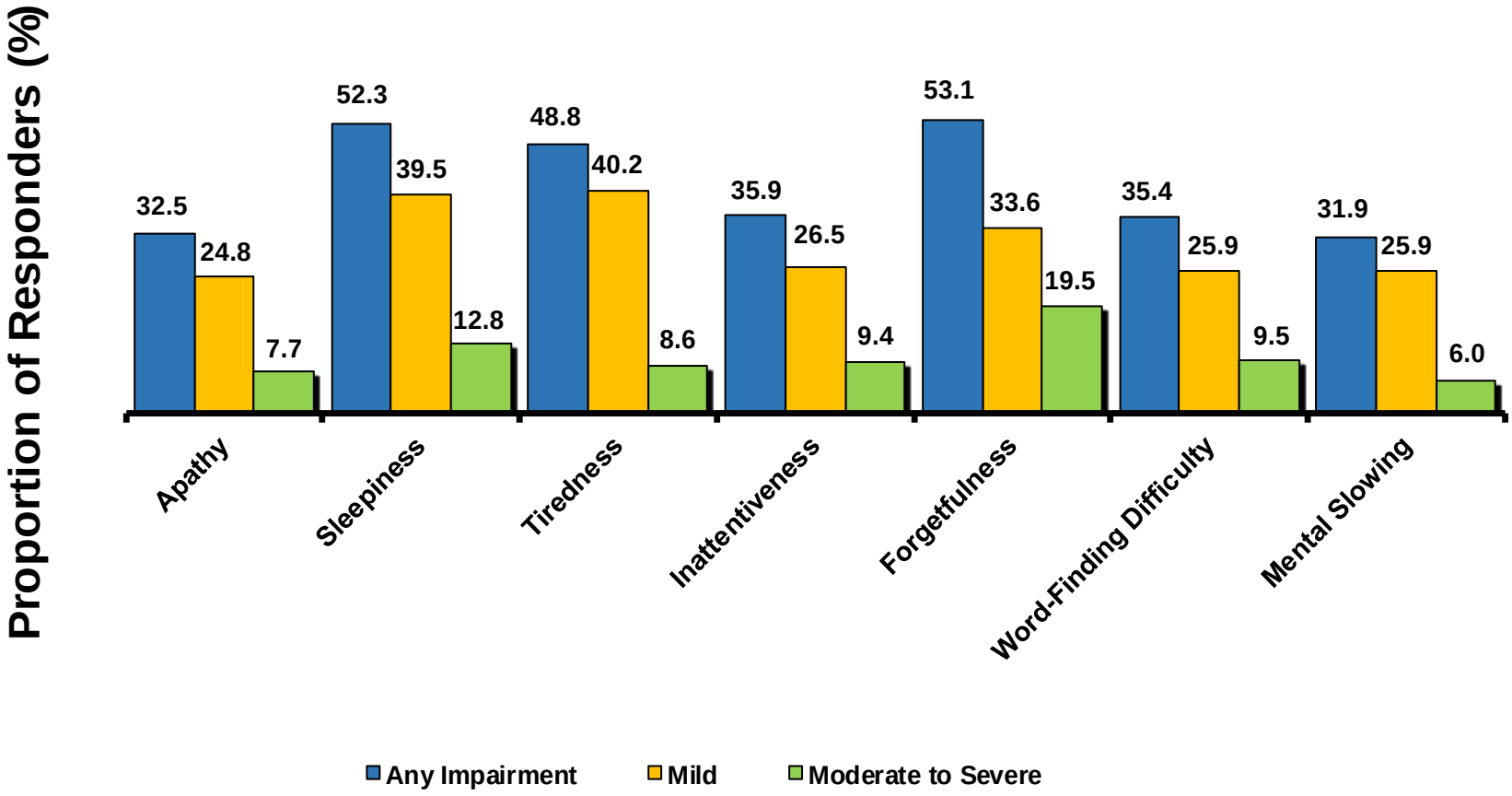
McClintock,S.M., et al., *J Clin Psychopharmacol*. 2011 Apr; 31(2): 180–186. doi: 10.1097/JCP.0b013e31820ebd2c
Nierenberg, A.A., et al., Psychological Medicine (2010), 40, 41–50. doi:10.1017/S0033291709006011

Most Common Symptoms in Non-Remitted Responders to Citalopram



McClintock,S.M., et al., *J Clin Psychopharmacol*. 2011 Apr; 31(2): 180–186. doi: 10.1097/JCP.0b013e31820ebd2c
Nierenberg, A.A., et al., Psychological Medicine (2010), 40, 41–50. doi:10.1017/S0033291709006011

Proportion of MDD Subjects with Residual Physical and Cognitive Deficits (N=117)



Fava M et al, *J Clin Psych* 2006; 67: 1754-1759

Duration of presence of DSM-IV (residual) symptoms during major depressive episodes (MDEs) and non-major depressive periods (non-MDEs)

Proportion of time that patients met DSM-IV criteria per symptom cluster

	During total follow-up	MDEs (n=481)	Non-MDEs (n=497)
Depressed mood/diminished interest	0.58 (0.25) ; 0.56 (0.50–0.72)	1.00 (0.00) ; 1.00 (1.00–1.00)	0.21 (0.27) ; 0.08 (0.00–0.36)
Cognitive problems	0.66 (0.30) ; 0.71 (0.50–0.97)	0.94 (0.20) ; 1.00 (1.00–1.00)	0.44 (0.37) ; 0.40 (0.08–0.78)
Lack of energy	0.60 (0.29) ; 0.61 (0.46–0.83)	0.90 (0.23) ; 1.00 (0.98–1.00)	0.35 (0.34) ; 0.24 (0.02–0.61)
Sleeping problems	0.61 (0.30) ; 0.63 (0.43–0.85)	0.85 (0.27) ; 1.00 (0.77–1.00)	0.39 (0.34) ; 0.32 (0.07–0.65)
Worthlessness/guilt	0.45 (0.32) ; 0.46 (0.15–0.68)	0.70 (0.36) ; 0.91 (0.45–1.00)	0.22 (0.30) ; 0.05 (0.00–0.42)
Eating problems	0.36 (0.31) ; 0.32 (0.05–0.57)	0.53 (0.39) ; 0.57 (0.13–0.99)	0.21 (0.28) ; 0.07 (0.00–0.36)
Psychomotor problems	0.24 (0.29) ; 0.09 (0.00–0.41)	0.35 (0.37) ; 0.23 (0.00–0.67)	0.14 (0.26) ; 0.00 (0.00–0.13)
Death ideations	0.24 (0.29) ; 0.09 (0.00–0.42)	0.37 (0.39) ; 0.25 (0.00–0.71)	0.11 (0.22) ; 0.00 (0.00–0.09)
Overall severity (range 0–9)	4.13 (1.65) ; 4.21 (3.36–5.00)	6.39 (0.88) ; 6.36 (5.71–7.00)	2.12 (1.36) ; 2.06 (0.98–3.18)

Conradi, H.J., et al.,*Psychological Medicine* (2011), 41, 1165–1174. Cambridge University Press 2010 doi:10.1017/S0033291710001911

CPFQ Scores in MDD Remitters and Non-Remitters

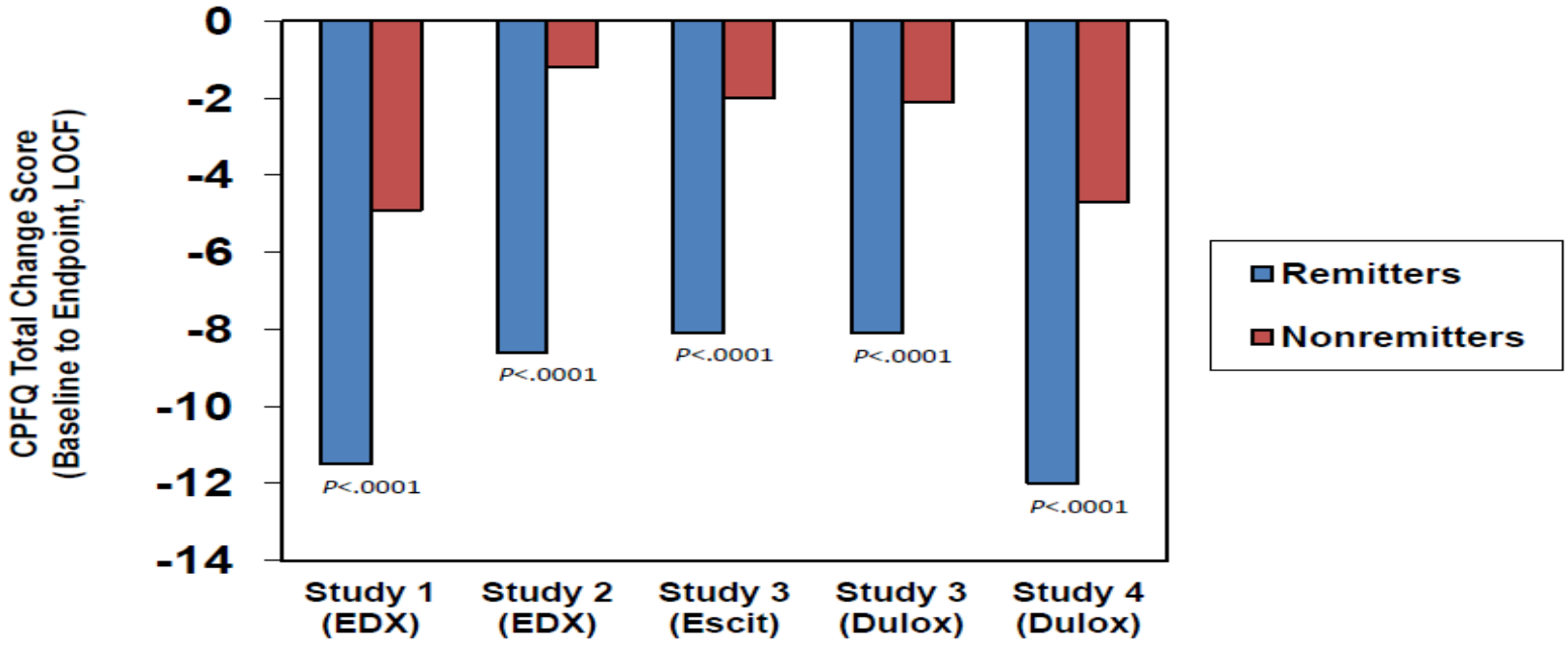


Figure 1. CPFQ total change scores for remitters vs. nonremitters.
Abbreviations: CPFQ = Cognitive and Physical Functioning Questionnaire; Dulox = duloxetine; EDX = edivoxetine; Escit = escitalopram; HAMD-17 = GRID Hamilton Rating Scale for Depression, 17-item; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale.
Note: In Studies 1, 2, and 3, remission was defined as MADRS total score ≤10. In Study 4, remission was defined as HAMD-17 total score ≤7.

Baer et al, *Annals of Clinical Psychiatry*, 2014;26(4):270-280

Functional Consequences of Cognitive Deficits in Depression

Functional Impairments in MDD

- Functional impairment has been part of diagnostic criteria
- "*Symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning*" (from DSM 5)
- Amount of disability and dysfunction exceeds that seen in many other common, chronic illnesses
- Areas of impairment include:
  - Physical
  - Psychosocial
  - Occupational
  - Quality of life
- Important to identify the contribution of cognition to these functional impairments

Greer TL et al. CNS Drugs 2010;24:267-84

Cognition Mediates Function

- Increasing evidence associating impaired cognition with impaired function
- Many associations are independent of depressive symptom severity
- No consensus to date on specifying the relationship between particular cognitive domains and particular functional domains
- Most data exist in work, occupational functioning

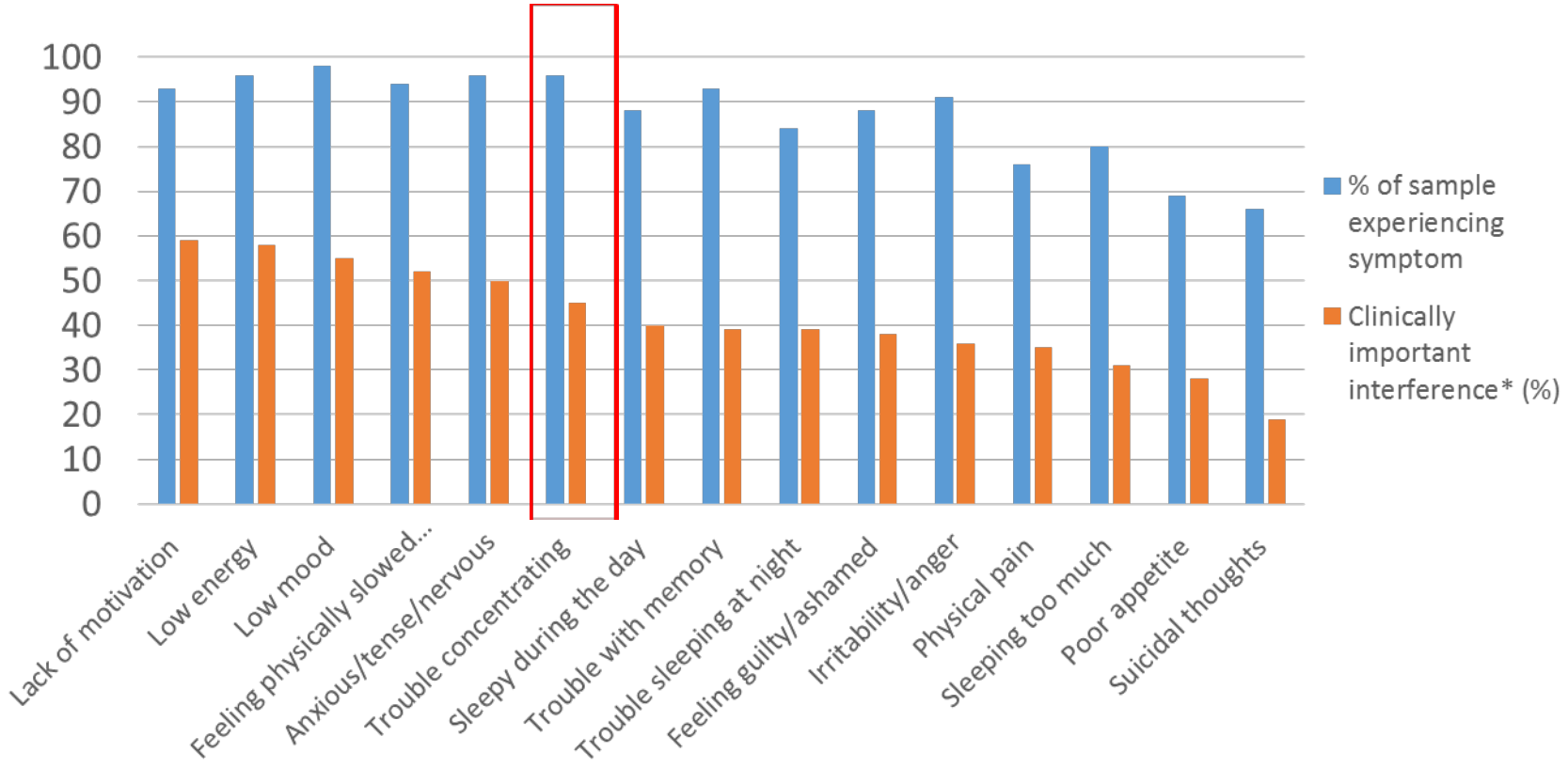
Greer TL, Hatt CR. Implications of Cognitive Impairments on Functional Outcomes in Major Depressive Disorder. In McIntyre R and Cha D (Eds.), Cognitive Dysfunction in Major Depressive Disorder. In press.

MDD in the Workforce

- On average, depression adds approximately 4-hours per week to health-related lost productive time
- Approximately one-tenth of US workforce reports being depressed
- Over three-fourths of those depressed report some loss in productivity

Source http://www.ncbi.nlm.nih.gov/pubmed/12813119

Self-reported Depressive Symptoms Interfering with Work Functioning



*Defined as a response of "Very much" or "So much that I had to stop working" to the following question: "In the past week, how have the following symptoms interfered with your ability to work?"

Lam R.W. et al., *Depression Research and Treatment.Volume* 2012, doi:10.1155/2012/630206

Relationship between Changes in Functioning (SDS) and Cognition (CPFQ) in MDD Patients with Residual Apathy

- Correlation between SDS and CPFQ total scores at baseline in patients with MDD and residual apathy: 0.55
- Correlation between SDS and CPFQ change in total score from baseline to endpoint in patients with MDD and residual apathy: 0.54 $p < 0.05$.

Model	Label	Standardized Coefficient	*p*-value[a]	Ordinary Coefficient	R-square
Change in SDS total score					0.67
	Intercept	0.00	<0.001	−10.27	
	Treatment	−0.03	0.339	−0.40	
	Baseline SDS total score	−0.71	<0.001	−0.78	
	Baseline CPFQ total score	0.69	<0.001	0.84	
	Change in CPFQ total score	0.77	<0.001	0.85	

Rothschild et al, *Comprehensive Psychiatry* 55 (2014) 1–10

Remission with no residual symptoms results in better long-term social function

Comparison of long term social outcome after remission below and residual symptoms in the Cambridge follow up study

Table 2. Comparison of long-term social outcome after remission below and with residual symptoms in the Cambridge follow-up study

	Remission below residual symptoms (n = 40)	Remission with residual symptoms (n = 19)	p value[a]
Social and occupational functioning over follow-up (%)			
>1 year lost from work after index remission	33	63	0.06
Modified longitudinal SAS over follow-up period (%)			
Good or fair longitudinal work functioning	81	42	0.010
Good or fair longitudinal marital functioning	81	44	0.018
Good or fair longitudinal parental functioning	94	86	1.0
Modified SAS at follow-up (SD)			
Mean social functioning over all subscales	1.7 (0.4)	2.2 (0.5)	0.003
Mean friction subscale	1.6 (0.6)	1.8 (0.6)	0.23
Mean dependency subscale	1.6 (0.5)	2.1 (0.8)	0.012
Mean interpersonal behaviour subscale	1.6 (0.4)	1.8 (0.5)	0.053
Mean performance subscale	1.9 (0.7)	2.5 (0.7)	0.003
Mean work subscale	1.3 (0.5)	1.9 (0.7)	0.013
Mean social/leisure subscale	1.7 (0.5)	2.3 (0.5)	0.002
Mean extended family relationship subscale	1.4 (0.4)	1.7 (0.5)	0.033
Mean marital relationship subscale	1.9 (0.4)	2.0 (0.5)	0.33
Mean parental functioning subscale	1.7 (0.8)	2.0 (0.3)	0.56

[a]Student's *t*-test for continuous variables; χ^2 or Fisher's exact test for categorical variables; SAS = Social Adjustment Scale.

Kennedy, N., et al., *Bipolar Disorders*. 2007: 9: 25-37

Association between symptom measurement and cognition in depression

Cognitive symptoms are not closely assessed with traditional symptom rating scales

- MADRS, HRSD, PHQ-9- only 1 or 2 items score cognitive function
- Routine Rating Instruments provide an unbalanced picture of depression severity, improvement, and recovery

Relationship Between Depressive and Cognitive Symptoms in MDD

TABLE.
Correlations Among Specific Symptoms Recorded by the HANDS and the CPFQ

CPFQ	Apathy/ Motivation	Wakefulness/ Alertness	Energy Level	Focus/Sustain Attention	Memory/ Recall	Word Finding Ability	Sharpness/ Mental Acuity
HANDS							
Fatigue	.24	.35*	.42	.32*	.45	.09	.23
Self-Blaming	.02	.01	–.04	–.09	–.04	–.02	–.03
Appetite	.11	–.12	.08	.04	–.04	.06	–.06
Sleep	–.04	–.07	.26	.09	–.12	.02	–.03
Hopelessness	.23	.13	.09	.18	.00	–.05	.09
Blue	.34*	.27	.27	.29	.04	.00	.18
Interest	.42*	.28	.29	.29	.08	.14	.24
Worthlessness	–.06	.13	.08	.04	.01	.049	.19
Suicide Thoughts	.10	.15	.09	.27	.17	.13	.11
Concentration/Making Decision	.32*	.29	.30	.52*	.29	.26	.38*

* $P<0.0007$

HANDS=Harvard Department of Psychiatry National Depression Screening Day Questionnaire; CPFQ=Cognitive and Physical Functioning Questionnaire; MGH=Massachusetts General Hospital.

Pedrelli P, Baer L, Iosifescu DV, Fava M. *CNS Spectr.* Vol 15, No 1. 2010.

Next Steps

- Targeted Treatments
- Incorporating Functional Measures into Definition of Remission

Targeted Treatments: An Example

- Treatment with Exercise Augmentation for Depression (TREAD) study
  - Primary results previously published in May 2011 issue of Journal Clinical Psychiatry
  - Remission rates after exercise augmentation of antidepressant treatments were 28.3 % and 15.5 % in high (16 KKW) and low (4 KKW) dose exercise groups

Cognitive impairment improves with exercise

- Cambridge Neuropsychological Test Automated Battery (CANTAB)
- Assess:
  - Attention
  - Visual memory
  - Executive function/Set shifting and working memory
  - Executive function/Set planning

Greer TL, Grannemann BD, Chansard M, Karim AI, Trivedi MH. *Eur Neuropsychopharmacol*. 2015 Feb;25(2):248-56.

Cognitive impairment improves with exercise

- 39 patients, 20 in low exercise (4KKW) and 19 in high exercise (16KKW) groups
- High dose exercise improves spatial memory
- No significant correlation between depression severity (IDS-C score) and improvement on cognitive task

Greer TL, Grannemann BD, Chansard M, Karim AI, Trivedi MH. *Eur Neuropsychopharmacol*. 2015 Feb;25(2):248-56.

Spatial Working Memory Performance Following Exercise Augmentation

Greer TL, Grannemann BD, Chansard M, Karim AI, Trivedi MH. Dose-dependent changes in cognitive function with exercise augmentation for major depression: results from the TREAD study. *Eur Neuropsychopharmacol*. 2015 Feb;25(2):248-56. doi: 10.1016/j.euroneuro.2014.10.001.

Redefining our definition of improvement

*For MDD, **remission** is the recommended goal of treatment*

Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder, *Neuropsychopharmacology* 2006 Sep; 31: 1841-53

Remission – defined

Clinically

- Absence of significant MDD symptoms for ≥ 2 months
- *Improvement in Function, Work Productivity and Cognition*

In Research

- 17-item Hamilton Rating Scale for Depression (HRSD17) score **< 7**
- Montgomery-Asberg Depression Rating Scale (MADRS) score **< 10**
- Quick Inventory of Depression Symptomatology (QIDS) score **< 5**

Traditional Outcome Ratings do not measure cognition adequately

Functional Recovery

- Unlike symptom remission, no consensus on how to define functional improvement or recovery
- Studies usually compare pre- to post- treatment/ intervention improvement
- Clinically significant change analyses vs. normative comparison
- Improved Cognition
- Return to Productive Work

Clinically Significant Change

- Methods outlined by Jacobson and Truax
  - Change after treatment is not accounted for by chance – **statistically significant**
  - Post-treatment score falls in the range of normal functioning – **clinically significant**

CANMAT Consensus Recommendations for Functional Outcomes in Major Depressive Disorder

- All stakeholders should recognize the clinical significance of functional outcomes in the management of MDD.
- Valid and reliable tools for measuring functional outcomes should be developed, evaluated, and disseminated.
- Clinical trials should be designed with functional outcomes as primary or co-primary outcomes.
- Stakeholders involved in funding, regulation, and KT of clinical trials should promote and ensure the inclusion of functional outcomes.
- Measurement-based care should incorporate functional outcome measures.
- Research about functional outcomes should be shared widely through integrated KT strategies.

Lam R.W. et al., *Annals of Clinical Psychiatry*. Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder 2015;27(2):142-149

Conclusions

- 40% to 55% of adults with MDD present with either subjective or objectively defined cognitive dysfunction
- The presence of cognition dysfunction in MDD is associated with greater illness severity and poorer functioning than MDD alone
- MDD patients with cognitive dysfunction are less likely to improve with placebo than MDD patients without it

Recommendations

- Target functional recovery including cognitive dysfunction in clinical treatment
- Evaluate:
  - specific impairments across domains (e.g. cognitive function)
  - general satisfaction with life (quality of life)
  - influence of somatic symptoms (e.g. sleep/fatigue, pain)
  - influence of sociodemographic variables
- Assess for an adequate period of time
- Select treatments and/or treatment regimens that maximize functional recovery
- Consensus is needed on how best to define

Thank You